

## Global Precision Oncology: A Call to Action on Expanding Access to Targeted Cancer Therapies

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Over the next half-century, the number of cancer deaths in low- and middle-income countries (LMICs) will eclipse those in high-income countries. This rising disease burden is unfortunately paired with a widening disparity in access to the most effective targeted therapies. At the health systems level, lack of diagnostic ability, inadequate access to trained providers, and limited drug availability provide significant barriers to cancer care delivery. Effectively addressing these barriers requires a long-term “diagonal approach” to improve the robustness of a health system to diagnose and treat cancer [1]. However, increasing affordability and access to precision oncology therapies can extend life and palliate symptoms for individuals with advanced and incurable disease in the near-term. In this article, we outline an urgent call to action to improve access to precision oncology therapies in LMICs, drawing upon lessons from international efforts in oncology and infectious disease.

Substantial improvements in the affordability of HIV medications represent a working model for advancing access to high-cost precision oncology therapies in LMICs. In the 1990s, HIV medications cost \$10,000–\$15,000 per person per year. In contrast, a highly effective single-pill antiretroviral cocktail is now available in LMICs for \$75 per person per year. Improved affordability was related to inclusion of antiretrovirals in the World Health Organization (WHO) Model List of Essential Medicines (WEM) beginning in the early 2000s. In parallel, the WHO's prequalification program incentivized generic companies to develop HIV drugs and facilitated access to medicines that met unified standards of quality, safety, and efficacy. Subsequently, generic competition has reduced the price for triple therapy by 67% [2]. Another important lesson from the model of HIV drug access is the importance of forming coalitions among governmental and nongovernmental organizations to improve price

negotiations and facilitate bulk drug purchasing. In 2016, an international coalition negotiated prices with generic drug makers to supply more than 92 LMICs with first-line HIV therapy for \$75 per person per year [3].

To make targeted cancer therapies affordable, it is imperative to promote inclusion on the WEM list [4, 5]. In 2017, the WEM list included only four targeted therapies, which has since expanded to eight therapies in 2019. These therapies include targeted antibodies such as rituximab and trastuzumab, as well as small molecule compounds like imatinib and erlotinib. In particular, priority should be given to drugs with greater efficacy than the current medications listed. One notable example of this is the lung cancer targeted therapy, osimertinib, which has significantly better survival and tolerability than earlier generation inhibitors in the same class. Second, drugs with the same efficacy and cost as existing drugs should be considered for inclusion to broaden the range of medications available for use. This is true for immune-checkpoint inhibitors, of which only nivolumab is currently included in the WEM. As a class, these medications may have an important role in the treatment of cancers arising in the setting of chronic viral infections, which are more prevalent in LMICs. Third, drugs that treat cancers not represented by existing therapies on the WEM should also be included, as noted in Table 1. In recent years, we have seen a rise in U.S. Food and Drug Administration approvals for precision oncology therapies and immunotherapies, encompassing an ever-broadening range of malignancies, which should be reflected in the medications listed in the WEM. At present, in an LMIC such as Botswana, certain targeted therapies (imatinib, rituximab, trastuzumab) are available publicly but are susceptible to supply chain limitations and stockouts and, in general, are more readily available in private hospitals, highlighting vast opportunities to improve equitable access to these therapies [6].

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**Table 1.** Targeted oncology therapies

Target	Therapy	Indication
HER2	Trastuzumab, <sup>a</sup> pertuzumab, lapatinib	HER2-amplified breast cancer
ER	Tamoxifen, <sup>a</sup> anastrozole, <sup>a</sup> exemestane	Hormone receptor positive breast cancer
AR	Abiraterone, enzalutamide, bicalutamide	Castration-resistant prostate cancer
PARP1	Olaparib, talazoparib	BRCA-1/2 mutant breast and ovarian cancer
CDK 4/6	Palbociclib, ribociclib, abemaciclib	Hormone receptor positive metastatic breast cancer
PD-1/PD-L1	Nivolumab, <sup>a</sup> pembrolizumab, avelumab, atezolizumab	Numerous cancers
BCR/ABL1	Imatinib, <sup>a</sup> dasatinib, <sup>a</sup> nilotinib, <sup>a</sup> bosutinib	CML, BCR/ABL1 rearranged ALL
PML/RAR	ATRA	Acute promyelocytic leukemia
IDH1	Ivosidenib	AML
IDH2	Enasidenib	AML
FLT3	Midostaurin, sorafenib, gilteritinib	AML
ALK	Crizotinib, alectinib, brigatinib, lorlatinib	Lung adenocarcinoma
EGFR	Erlotinib, <sup>a</sup> gefitinib, afatinib, osimertinib	Lung adenocarcinoma
ROS1	Crizotinib, lorlatinib	Lung adenocarcinoma
BRAF	Vemurafenib, dabrafenib, encorafenib	Melanoma, lung adenocarcinoma
NTRK	Entrectinib, larotrectinib	Numerous cancers with NTRK alterations

Examples of targets, and drug names of therapies along with common cancer indications.

<sup>a</sup>Drugs currently listed in the 2019 World Health Organization Essential List of Medicines.

Abbreviations: AML, Acute myeloid leukemia; AR, androgen receptor; CML, chronic myelogenous leukemia; ER, estrogen receptor; PD-1/PD-L1, programmed cell death protein-1/programmed cell death ligand-1.

The cost of precision oncology therapies can be on the order of thousands of dollars a month. However, the approval of biosimilars for certain antibody-based therapies and the approval of generic medications will contribute to more affordable options becoming available in the future. Adding these therapies onto the WEM list could motivate international collaborations and partnerships focused on cost reduction. The first of its kind, Access Accelerated, a partnership of the World Bank Group and the Union for International Cancer Control, has embarked on an asset-based approach, pledging to develop sustainable programs in LMIC cities with a population greater than one million to implement effective diagnostics and treatments for patients at risk of or diagnosed with cancer. Finally, building local capacity by investing in the development of pharmaceutical companies and drug

manufacturers in LMICs will be critical to expanding the production and supply of therapeutic compounds.

In parallel to expanding the WEM list, short-term strategies to promote drug accessibility involve partnering with pharmaceutical companies to facilitate drug donation and distribution. A highly successful program focused on expanded access to targeted cancer therapies involves the work of The MAX Foundation with chronic myelogenous leukemia (CML). The foundation has partnered with pharmaceutical companies around the world to provide targeted CML therapies for little to no cost while promoting local health system strengthening by developing a global network of physicians and cancer centers who can interpret labs, diagnose patients, and write appropriate prescriptions in LMICs [7, 8].

Delivering precision oncology care requires the use of readily available molecular diagnostics. Currently, automated polymerase chain reaction (PCR)-based assays are routinely employed for the detection of tuberculosis and emergent tuberculosis therapy resistance [9]. Similar assays have been deployed in resource-constrained settings to diagnose and manage CML and can be expanded to detect a panel of highly actionable genetic alterations [10, 11]. In areas where PCR-based assays are not feasible, standard immunohistochemistry and fluorescent in situ-hybridization represent alternative options for genotyping of a limited set of actionable molecular alterations, including mismatch repair gene deficiency, programmed cell death ligand-1 expression, HER2 amplification, hormone receptor expression, and ALK rearrangement [12]. In parallel, hospital twinning strategies, clinical oncology fellowship exchange programs, and virtual precision oncology tumor boards have been employed and can be expanded to build a workforce with expertise around diagnosis, precision oncology focused therapeutic interventions and medication monitoring [13–15]. In the long-term, these efforts will promote capacity building and research leading to sustainable cancer care programs in partner countries and overall health systems strengthening.

In the past several decades, we have seen remarkable improvement in drug access for HIV treatment. In a similar fashion, there is an equity imperative to urgently push for affordable access to precision cancer therapies in areas with a rising burden of disease. As a first step, we must add crucial and highly effective targeted therapies to the WEM list to encourage governments to prioritize the purchase of these medications and to push for partnerships and price negotiations that will make these effective and well-tolerated medications more affordable. Second, we must create a consortium of academic and nonprofit institutions focused on improving access to drugs. Last, and most importantly, we need to create multi-institutional twinning partnerships to support and implement appropriate diagnostics, therapeutic delivery, and monitoring. Our hope is that this three-step call to action would support the “diagonal model,” in which diagnostic capabilities, drug affordability, and availability are tackled in a unified and simultaneous fashion to address the rising burden of cancer in LMICs.

#### DISCLOSURES

The authors indicated no financial relationships.

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**For Further Reading:**

Roberto Jun Arai, Rodrigo Santa Cruz Guindalini, Andrea Sabina Llera et al. Personalizing Precision Oncology Clinical Trials in Latin America: An Expert Panel on Challenges and Opportunities. *The Oncologist* 2019;24:e709–e719.

**Implications for Practice:**

Precision clinical trials in oncology are studies that require candidates to have tumors with specific molecular alterations, which are considered the target for the trial experimental therapy. Because many molecular alterations are rare, fewer patients are enrolled. This has led to trials being forced to be multicenter and multinational, including trials in Latin America. This article discusses the challenges and opportunities to conduct precision oncology trials in Latin America, aiming to help sponsors and investigators to solve complex issues that ultimately lead to more of such trials being run in the region, potentially benefiting more Latin American patients with cancer.